Early Human Development 88 (2012) 21–26

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Skin conductance measurements as pain assessment in newborn infants born at 22–27 weeks gestational age at different postnatal age

Josanne Munsters [a,b], Linda Wallström [a], Johan Ågren [a], Torgny Norsted [a], Richard Sindelar [a,*]

[a] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[b] Radboud University Nijmegen, Department of Paediatrics, Medical Centre Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 3 February 2011
Received in revised form 14 June 2011
Accepted 17 June 2011

Keywords:
Skin conductance
Pain assessment
Stress response
Extremely preterm infants

ABSTRACT

Background: To assess pain or stress in newborn infants submitted to intensive care is important but difficult, as different observational pain scales are not always reliable in premature infants. As an indicator of pain, skin conductance (SC) measurements have detected increased sweating in newborn infants >28 gestational age (GA) submitted to heel lancing.
Objective: To measure SC during heel lancing and routine care in newborn infants, born at 22 to 27 GA, with special relation to postnatal age (PNA).
Methods: In six infants <28 + 0 GA and 4 infants ≥28 + 0 GA spontaneous SC activity and behavioural state (Neonatal Pain Agitation and Sedation Scale (N-PASS)) was measured before, during and after each intervention. Measurements were repeated in each patient at different PNA.
Results: Baseline SC prior to intervention took longer time to stabilise and was higher in <28 than in ≥28 + 0 PNA. The combination of heel lancing and squeezing gave an increased SC in <28 PNA, whereas heel lancing alone gave the same SC response in ≥28 + 0 PNA. A possibly continued immature response in SC measurements was not observed. Oral glucose admission prior to heel lancing increased SC. Routine care did not give any changes in SC. Except during orogastric tube placement no signs of discomfort or pain could be detected by the neonatal pain, agitation and sedation scale (N-PASS) in <28 PNA.
Conclusion: Changes in SC could be detected in infants at <28 + 0 PNA and related to the combination of heel lancing and squeezing. A maturational development of the SC was observed in infants born <28 GA. SC seems to be able to differentiate between pain and discomfort.

1. Introduction

Extremely preterm infants are subjected to an intensive care that is characterised by many painful procedures and environmental disturbances. To assess pain or stress in newborn infants submitted to intensive care is important in order to evaluate effective pain management and thereby reduce harmful short and long term effects of pain; specifically brain development [1]. Many studies have been performed to assess pain in preterm infants, but it has been difficult to find a "golden standard" to measure the pain or discomfort they might experience during potentially painful procedures in the intensive care unit [1,2]. As both physiological and observational pain scores developed for more mature infants have been shown to have their limits in scoring pain in premature infants, efforts have been made to develop new method for pain assessment [2–7].

Emotional sweating is a physical reaction to emotive stimuli like stress, anxiety, fear and pain that can occur over the whole body surface, but is most evident on palms, soles and in the axillary region [8]. Unlike thermoregulatory sweating, it arises independently of ambient temperature and decreases during sleep and relaxation [8]. Emotional sweating of palms and soles occurs already in newborn infants [9].

A sensitive method of measuring skin conductance (SC) has been developed, based on stress induced sweating. SC is determined by the number and the activity of sweat glands, and their activity is stimulated by the sympathetic nervous system [10–14]. When pain is experienced, sweat glands are stimulated by sympathetic excitatory efferent neurons and sweat is released within 1–2 s whereby SC increases due to skin resistance reduction [10,15]. When the painful stimulus is taken away, sympathetic activity decreases and the sweat is reabsorbed and evaporated, followed by a decrease in skin conductance. The sympathetic neural firing resulting in excretion of the sweat gland can be depicted as one skin conductance peak [10,16]. The number of skin conductance peaks correlates directly to the firing rate in the sympathetic nerves of the skin [17]. Previous studies in

Abbreviations: GA, gestational age; SC, skin conductance; PNA, postnatal age; N-PASS, neonatal pain agitation and sedation scale; TEWL, transepidermal water loss.

* Corresponding author. Department of Women's and Children's Health, Uppsala University, University Children's Hospital, 751 85 Uppsala, Sweden. Tel.: +46 18 611 96 27; fax: +46 18 55 40 79.
E-mail address: Richard.Sindelar@kbh.uu.se (R. Sindelar).

0378-3782
doi:10.1016/j.earlhumdev.2011.06.010

infants born at >28 GA have shown that skin conductance increased with the level of behavioural state [18]. To our knowledge no SC studies have been performed in premature infants born at <28 GA.

The aim of this study was to find out at which GA preterm newborn infants start to react to potential painful or discomforting procedures by emotional sweating and how this response changes with different PNA.

2. Methods

2.1. General

The study was performed at the neonatal care unit, Uppsala University Children's Hospital in Uppsala, Sweden. SC was measured when infants were exposed to heel lancing for routine blood sampling, feeding, orogastric tube placement and routine care. Observing the infants with N-PASS, an observational scale used as routine assessment of pain in this neonatal unit, included behavioural changes associated with pain perception [19].

2.2. Patients

Ten preterm infants were recruited from the neonatal care unit, Uppsala University Children's Hospital during a period of 3 months. Infants who were in a haemodynamically stable condition and did not receive any anaesthetics that might have interfered with their pain response to planned clinically indicated heel lancing were eligible for participation. No patients recruited were excluded.

In total there were six girls and four boys. The infants were born between 22 + 4 and 34 + 3 weeks (median: 28 + 1 weeks) GA and at the time of the study they were between 1 and 47 days PNA (median: 15 days).

Patients were divided into 2 groups: <28 weeks GA and >28 weeks GA. These two groups were analysed in four different ways: <28 weeks GA, >28 weeks GA, <28 weeks PNA and >28 weeks PNA.

Median weight at birth was 633 g (range: 437 g–920 g) <28 weeks GA and 2191 g (range: 1727 g–2910 g) ≥28 weeks GA. At the time of participation in the study the median weight <28 weeks PNA was 548 g (range: 522 g–580 g). Mean APGAR-scores were 4, 6 and 8 (respectively after 1, 5 and 10 min) in infants <28 weeks, and 7, 9 and 9 in infants >28 weeks.

All the patients <28 weeks GA were artificially ventilated. None of the patients >28 weeks GA needed respiratory assistance. The study was approved by the Ethics Committee of the Medical Faculty at Uppsala University. Parental consent was obtained before the infant was included in the study and reconfirmed before each subsequent measurement.

2.3. Methods and measurements

In this longitudinal cohort study SC was measured with the Med-Storm Pain Monitor (Medstorm Innovations, Oslo, Norway) [9]. Three electrodes were applied on the infant's foot and measurements of SC, number of fluctuations within the mean SC per second (NFSC) and amplitude of NFSC were analysed. The counter current electrode was placed on the medial right side of the foot, the measuring electrode was placed midway between the first phalanx and a point directly beneath the ankle and the reference voltage electrode was placed on the dorsal side of the foot (Fig. 1). The analysed values are peaks/s (the rate of firing in the sympathetic nerves), average amplitude (mean peaks) and area under curve (forcefulness of sympathetic nerve firing). The N-PASS was used to analyse behavioural state, irritability, facial expression, tone and vital signs in preterm infants, and performed simultaneously by a care giving nurse and the researcher [19]. The N-PASS was specifically chosen as an observational assessment tool because it is the most commonly used tool in our neonatal ward. Transepidermal water loss (TEWL) was measured in three patients at <28 weeks GA in order to define the maturational status of the skin, a factor that might interfere with the emotional sweating [20].

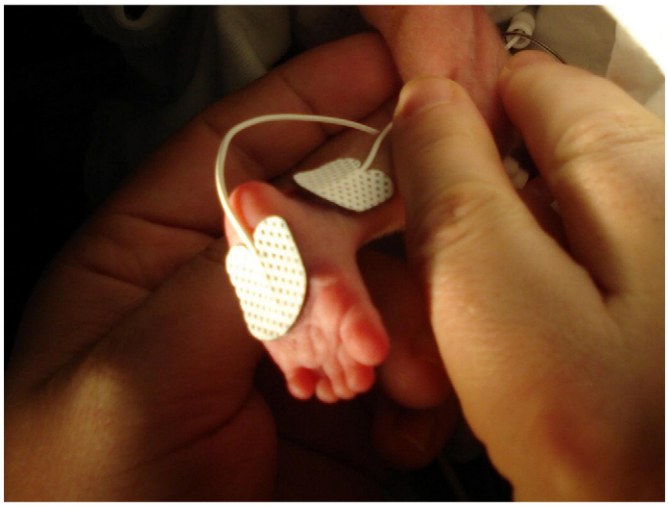

Fig. 1. Application of skin conductance measurement electrodes on the foot of a 26 PNA weeks infant.

Heart rate and saturation were measured in patients <28 GA and PNA before, during and after each registration period.

2.4. Study design

Measurements were performed during heel lancing for routine blood collection and during feeding, orogastric tube placement and routine care such as diaper change, feeding and auscultation.

Electrodes were applied to the infants' foot 5 min before the intervention.

All heel lancing was scheduled at least 1 h after feeding. All infants received 0.5 ml 30% oral glucose before heel lancing according to established unit policy, except for one extremely preterm boy with insulin infusion due to hyperglycaemia. Behavioural state (N-PASS) and skin conductance activity were measured for 2 min before, during, and for 2 min after the intervention.

During heel lance electrodes were attached to the opposite foot to prevent any artefacts by touching the measurement electrode. Measurements started at least 1 min before the glucose was given. After the heel lance and the squeezing period the measurement continued for at least 2 min.

Orogastric tube placement was performed within a minute. Measurement of SC and of N-PASS continued for a couple of minutes. Feeding was done with a syringe and in very small portions, during at least five and at most 30 min. After feeding the measurement continued for at least 3 min.

Skin conductance registrations were made for approximately 10 min. Auscultation with a stethoscope was also measured, as was the effect of tactile stimuli (such as caressing the child and kangaroo mother care), sounds (in the ward) and warm versus cold (water bags on the infants' feet before heel lancing and application of a cold stethoscope).

The groups were analysed in four different ways: <28 weeks GA and >28 weeks GA independent of PNA; <28 PNA and >28 weeks PNA independent of GA. The means for each analysis were put into tables and figures.

2.5. Method of analysis

Measurements of SC were analysed by taking thirty-second intervals of which the mean peaks/s and average peak were calculated. The thirty

second time intervals were chosen because the time between glucose given prior to heel lancing and the start of heel lancing was approximately 30 s and thereby enabling comparisons of all registered intervals. The first baseline was defined as the thirty-second interval before glucose administration. For the heel lancing one period of thirty seconds was taken, because right after the heel lance the nurses began squeezing the foot. The second baseline was defined as the interval where the peaks/s and the average peak lowered significantly or returned to zero.

2.6. Statistics

Repeated-measures analysis of variance was used to test for differences between measurements made during the various interventions studied. Student's *t-test* for two-sided paired observations was applied whenever a difference was detected by analysis of variance, and differences were considered significant at $p<0.05$.

3. Results

All infants <28 weeks GA (n = 6) were on theophylline and infants >28 weeks GA (n = 4) were not on any medication at the time of measurements (Table 1). Baseline SC prior to intervention took longer time to stabilise – approximately 5 min – and was higher in <28 than in ≥28 + 0 PNA (0.07 ± 0.03 peaks/s vs. 0.01 ± 0.01 peaks/s: $p = 0.037$). Irrespective of the duration of the heel lancing procedure, the skin conductance after painful stimuli also took a longer time to return to baseline levels in <28 than in ≥28 + 0 weeks PNA (123 ± 16 vs. 21 ± 9 s; $p<0.0001$).

The combined heel lancing and squeezing gave an increased SC in <28 PNA (Fig. 3B), whereas heel lancing alone gave the same SC response in ≥28 + 0 PNA, which was maintained at the same level during squeezing (Figs. 2 and 3D). A possibly continued immature response to heel lancing and/or squeezing irrespective of PNA was not observed, as SC responses related to only GA was similar between <28 + 0 and ≥28 + 0 weeks GA (Figs. 2, 3A and C). All infants tended to have an increased SC to glucose administration prior to heel lancing: in <28 PNA at the same level as maximal SC but in ≥28 + 0 PNA lower than heel lancing and squeezing (Fig. 3B and D). Other interventions, such as tactile stimuli, orogastric tube placement, feeding, cold or warm stethoscope application did not result in any changes in SC.

Table 1
Demographic characteristics of the population studied.

Characteristics	Results	
	<28 GA	≥28 GA
Number of patients (n)	6	4
GA (weeks)	$24^{+4} \pm 1^{+5}$ [22^{+4}–26^{+6}]	$33^{+2} \pm 1^{+1}$ [33^{+0}–34^{+3}]
PNA (days)	21 ± 13 [3–47]	6 ± 5 (1–16)
Birth weight (grammes)	633 g. ± 179 (437–920)	2191 g. ± 529 (1727–2910)
Apgar scores		
1 min	4 ± 1.75 (2–7)	8 ± 0.8 (7–9)
5 min	7 ± 2.25 (4–9)	9 ± 0.95 (8–10)
10 min	8 ± 1.26 (6–9)	9 ± 0.96 (8–10)
Intraventricular haemorrhage (grade I–IV)	0	IV + I/II (n = 1)
Patent ductus arteriosus	6	0
Indomethacin	3	0
Operation	3	0
Medication		
Surfactant	6	0
Theofyllin	6	1
Vitamin A, D, C	1	0
Antibiotics	0	0
Saline substitution	5	0

The N-PASS was used as an observational scale to compare with the SC results. No signs of discomfort or pain could be detected with N-PASS in infants born at <28 GA during glucose administration, heel lancing with squeezing or routine care, except during orogastric tube placement. Even though the infants were in discomfort during orogastric tube placement, according to N-PASS (Table 2), no changes in SC were detected during this intervention.

Baseline heart rate did not vary significantly between patients but increased during the heel lancing procedure by more than 10 bpm. Saturation varied widely and sometimes went below 80% during intervention. Both heart rates and saturation levels returned to baseline soon after the heel lancing procedure was stopped.

4. Discussion

This study shows that a stress response to heel lancing can be detected with skin conductance measurements from 22 weeks GA.

Baseline levels of skin conductance prior to stimuli were higher in infants <28 weeks PNA than in infants ≥28 weeks PNA. One explanation could be the maturational aspect of the skin. The permeability of the skin gradually changes with GA and PNA as trans-epidermal water loss (TEWL) decreases in preterm infants during their first weeks of life [20,21]. However, TEWL does not cause bursts of excretion and the TEWL measurements in our study of infants <28 weeks PNA were constant and stable, and not related to pain evoked changes in skin conductance. Although measures were taken to exclude environmental disturbances during measurements of heel lancing and planned interventions, a higher state of stress cannot be excluded as a reason for the observed higher baseline level of skin conductance in our cohort of infants born <28 weeks GA and at ≥28 weeks PNA, as these infants might have been exposed to more painful procedures as part of their intensive care with possibly adverse effects on their immediate pain response [22–25]. On the other hand, a long-term effect on the pain response of <28 weeks GA is not fully consistent with the fact that their response to heel lancing with skin conductance measurements at >28 weeks PNA did not differ from infants born ≥28 weeks GA (see Fig. 3C and D), also supported by follow up studies on recovered biobehavioral responses to acute pain in former extremely low birth weight infants [26].

A prolonged pain response after heel lancing could be due to an immature sympathetic regulation or cortical pain processing, as shown in studies of preterm infants born after 25 GA where increases in cortical total haemoglobin concentrations after heel lancing were used as a measure of pain response and where maturational differences were detected [27,28]. Interestingly, Slater et al. propose a difference between spinal and cortical pain processing based on the fact that the amplitude and the duration of pain response is markedly higher for peripheral than central pathways in more immature infants, and that peripheral pathways do not necessarily imply a perceived pain [28–30]. Maturational similarities in both duration and amplitude between our skin conductance measurements and spinal pain processing seem to exist, but both the higher baseline activity prior to stimuli and the markedly lower baseline after stimuli indicates yet another pain response, further supported by the difference in SC response to potentially painful stimuli, i.e. heel lancing, and squeezing in the present study.

Infants <28 weeks PNA seemed to react more to the squeezing after the heel lancing, whereas the more mature infants reacted more strongly to the actual heel lancing procedure. A previously published study interpreted latency in facial response to heel lancing in newborn infants below 32 weeks PNA to be caused by less myelination and slower neurotransmission in immature subjects [31], an explanation feasible with the delayed response in our study to heel lancing in infants below 28 weeks PNA and consequently the overlapping of heel lancing and squeezing. However, the threshold for mechanical stimulation, as studied by flexion withdrawal reflex, has

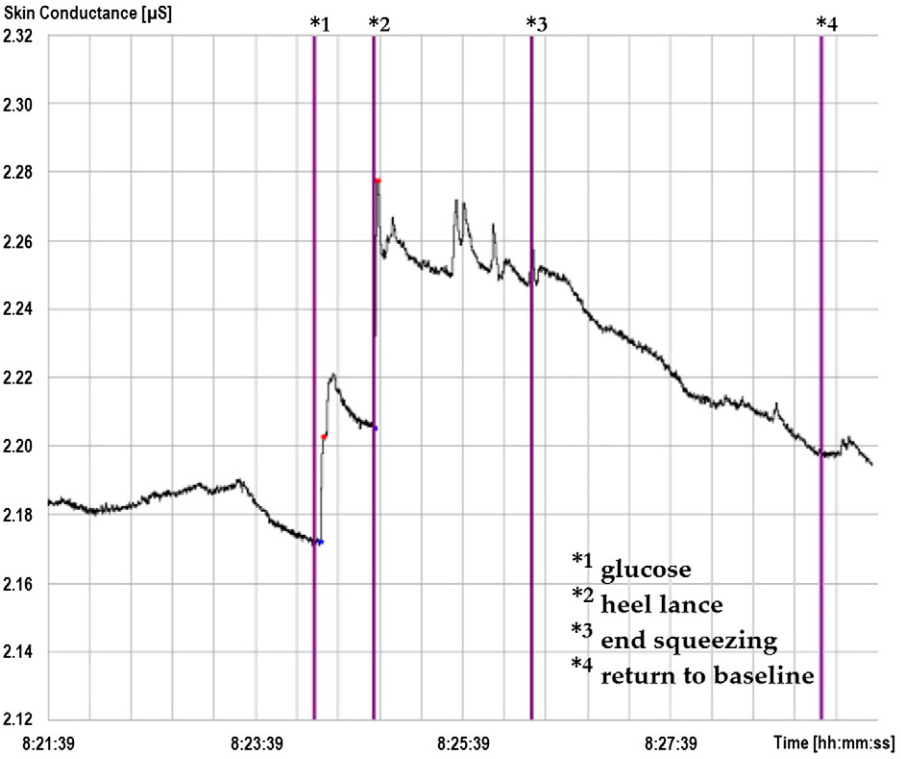

Fig. 2. Skin conductance registration (µS) in one infant <28 weeks GA at ≥27 PNA, with each intervention (*1–4) depicted over time (hh.mm.ss = hours.minutes.seconds).

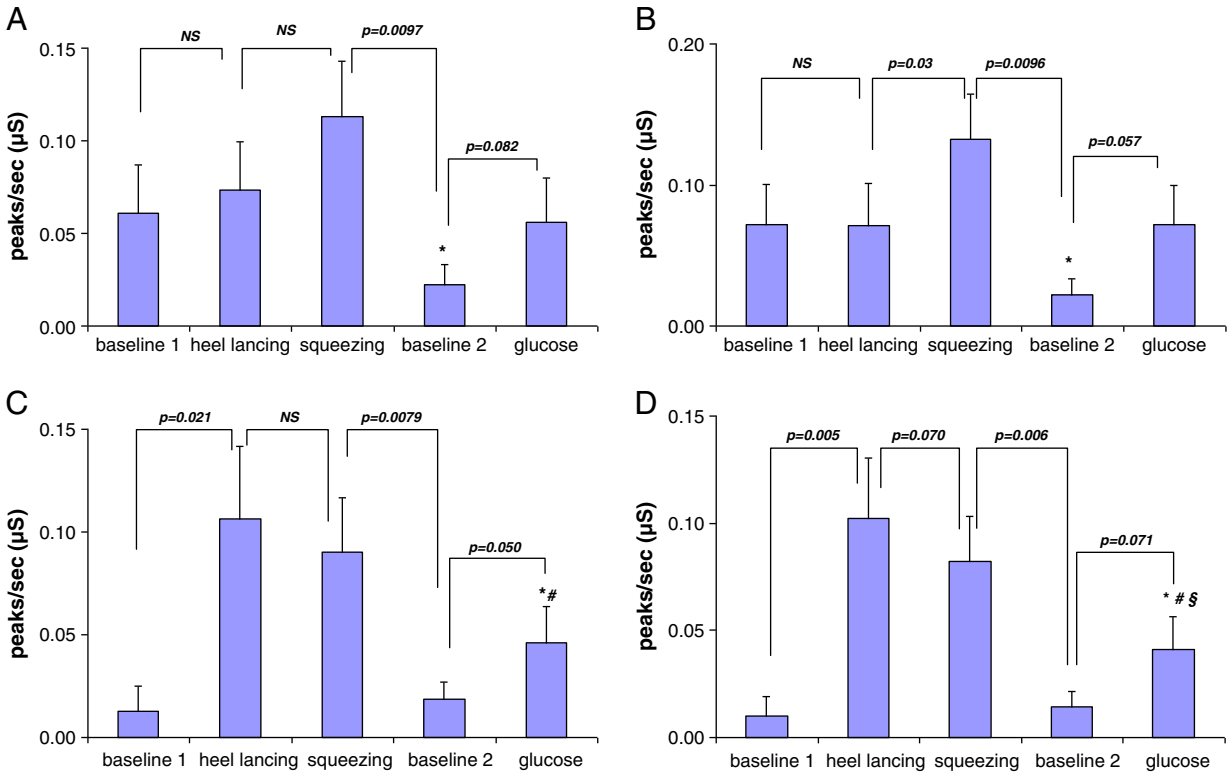

Fig. 3. (A) Skin conductance response to heel lancing in newborn infants <28 weeks GA. Error bars denoting standard error of mean. *$p = 0.036$ baseline 2 vs. heel lancing. (B) Skin conductance response to heel lancing in newborn infants <28 weeks PNA. Note the markedly lower baseline (baseline 2) after heel lancing and squeezing than prior (baseline 1) to heel lancing and squeezing. Error bars denoting standard error of mean. *$p = 0.039$ baseline 2 vs. baseline 1. (C) Skin conductance response (peaks/s) to heel lancing in newborn infants ≥28 weeks GA. Error bars denoting standard error of mean. *$p = 0.052$ glucose vs. heel lancing; #$p = 0.073$ glucose vs. squeezing. (D) Skin conductance response (peaks/s) to heel lancing in newborn infants ≥28 weeks PNA. Note the markedly increased response of peaks/sec during heel lancing and squeezing. Error bars denoting standard error of mean. *$p = 0.019$ glucose vs. heel lancing; #$p = 0.029$ glucose vs. squeezing; §$p = 0.044$ glucose vs. baseline 1.

Table 2
Mean N-PASS results <28 weeks PNA.

Assessment criteria	Mean score<28 PNA
Crying irritability	No cry with painful stimuli (−2)
Behavioural state	Arouses minimally to stimuli, little spontaneous movement (−1)
Facial expression	Mouth is lax, no expression (−2)
Extremities tone	Weak grasp reflex, ↓ muscle tone (−1)
Vital signs (HR/BP/SaO2)	<10% variability from baseline with stimuli (−1)

Premature pain assessment: +3 if <28 weeks gestation/corrected age.

been shown to be lower in preterm infants [32,33] and therefore a postponed response to heel lancing cannot be excluded from our data. Squeezing was not separated from the heel lancing procedure in the present study since there was no ethical disclosure for measuring SC during squeezing alone. Nevertheless, some of the normal care procedures of these infants included moderate pressure of the skin during SC measurements and these did not evoke an increase in SC.

All infants tended to respond with increased SC to oral glucose as related to baseline irrespective of GA or PNA (Fig. 3A–D). As this was an unanticipated finding, SC measurements for oral glucose are presented separately in all figures. Several randomised clinical trials have shown that oral sucrose reduces the behavioural pain response to subsequent routine care giving procedures as assessed by observational pain scales [34–36]. Since it was not our intention to challenge this view, neither a comparison with other oral agents, or an evaluation of the effectiveness of oral glucose on SC measurements were made. However, the effectiveness of sucrose as an analgesic drug has been questioned in studies where sucrose had no effect on spinal or cortical pain responses [37,38]. In our study no significant behavioural pain responses were observed during glucose administration (or heel lancing) although SC responses to glucose were detected, especially in infants ≥28 PNA weeks (Fig. 3D).

Behavioural state measured by the N-PASS was not a sufficient tool to compare the changes in SC measurements. Because of ventilatory support, orogastric and nasal tubes, it is difficult to observe discrete changes in facial expression as previously noted and nor can crying be observed in ventilated infants [39]. The N-PASS does correct for prematurity by adding three points in advance for inability to cry, little to no spontaneous movement and low muscle tone, but still it is difficult to interpret the results of this scale in extremely preterm infants. Future SC research should compare SC with other pain assessment tools such as cardiovascular response [40], near-infrared spectroscopy (NIRS) [27], withdrawal reflex [32], salivary cortisol [41] and EEG [42].

Although the limitation of this study is the small sample size, repeated measurements always showed a SC response related to heel lancing and squeezing, but not related to other stimuli included in the normal care of newborn infants. Other potentially stressful procedures should be studied in the future in combination with pain relieving interventions.

Evaluating stress response to painful stimuli in preterm infants might assist clinicians to provide the most effective pain management strategies, and thereby prevent the negative short and long term effects of pain [22,43–45]. Monitoring skin conductance may be a useful tool to do so. Nevertheless, artefacts are likely to occur, when infants move or electrodes become detached from the skin. Interference with other electrical monitoring such as EEG and ECG should also be excluded. Therefore it is important to observe the infants continuously in order to get a reliable SC measurement.

In conclusion, measurements of SC activity showed responses to heel lancing in preterm infants between 22 and 27 weeks GA with a maturational development related to PNA.

Conflict of interest

The authors have no conflict of interest to disclose.

Acknowledgements

This study was supported by grants from Her Royal Highness the Crown Princess Lovisa's Foundation for Children's Health, Stockholm and the Gillberg's Foundation, Uppsala. The authors thank the staff of the Intensive Care Unit of University Children's Hospital, Uppsala.

The authors are grateful to Professor Gunnar Sedin for support and help with arranging the research internship. They are also indebted to Barbro Kjällström and Maria Stålhammar for their skilled laboratory assistance.

References

[1] Gibbins S, Stevens B, McGrath PJ, Yamada J, Beyene J, Breau L, et al. Comparison of pain responses in infants of different gestational ages. Neonatology 2008;93:10–8.
[2] Coleman MM, Solarin K, Smith C. Assessment and management of pain and distress in the neonate. Adv Neonatal Care 2002;2(3):123–36.
[3] Hummel P, van Dijk M. Pain assessment: current status and challenges. Semin Fetal Neonatal Med 2006;11(4):237–45.
[4] Mathew PJ, Mathew JL. Assessment and management of pain in infants. Postgrad Med J 2003;79:438–43.
[5] McVey C. Pain in the very preterm baby: 'suffer little children?'. Pediatr Rehabil 1998;2(2):47–55.
[6] Gibbins S, Stevens B, Beyene J, Chan PC, Bagg M, Asztalos E. Pain behaviours in extremely low gestational age infants. Early Hum Dev 2008;84(7):451–8.
[7] Currie JM. Stress and pain relief in the care of the surgical neonate. Semin Pediatr Surg 2008;17(4):285–9.
[8] Wilke K, Martin A, Terstegen L, Biel SS. A short history of sweat gland biology. Int J Cosmet Sci 2007;29(3):169–79.
[9] Storm H. Skin conductance and the stress response from heel stick in preterm infants. Arch Dis Child Fetal Neonatal Ed 2000;83(2):143–7.
[10] Storm H. The development of a software program for analyzing skin conductance changes in preterm infants. Clin Neurophysiol 2001;112(8):1562–8.
[11] Christie MJ. Electrodermal activity in the 1980's: a review. J R Soc Med 1981;74: 616–22.
[12] Engelberg R. Relation of electrical properties of skin to structure and physiologic state. J Investig Derm 1977;69:324–7.
[13] Lidberg L, Wallin G. Sympathetic skin nerve discharges in relation to amplitude of skin resistance responses. Psychophysiology 1981;18(3):268–70.
[14] Hagbarth KE, Hallin RG, Hongell A, Torebjørk HE, Wallin BG. General characteristics of sympathetic activity in human skin nerves. Acta Physiol Scand 1972;84: 164–76.
[15] Storm H. Changes in skin conductance as a tool to monitor nociceptive stimulation and pain. Curr Opin Anaesthesiol 2008;21:796–804.
[16] Macefield VG, Wallin BG. The discharge behaviour of single sympathetic outflow in normotensive human sweat glands. J Autonom Nervous Syst 1996;61:277–86.
[17] Storm H, Shafiei M, Myre K, Raeder J. Palmar skin conductance compared to a developed stress score and to noxious and awakening stimuli on patients in anaesthesia. Acta Anaesthesiol Scand 2005;49(6):798–803.
[18] Storm H. Development of emotional sweating in preterms measured by skin conductance changes. Early Hum Dev 2001;62(2):149–58.
[19] Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. J Perinatol 2008;28(1):55–60.
[20] Agren J, Sjörs G, Sedin G. Transepidermal water loss in infants born at 24 and 25 weeks of gestation. Acta Paediatr 1998;87(11):1185–90.
[21] Sedin G, Hammarlund K, Strömberg B. Transepidermal water loss in full-term and pre-term infants. Acta Paediatr Scand Suppl 1983;305:27–31.
[22] Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G, Marchand S. Preterm births: can neonatal pain alter the development of endogenous gating systems? Eur J Pain 2008;12(7):945–51.
[23] Grunau RE, Weinberg J, Whitfield MF. Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. Pediatrics 2004;114(1):77–84.
[24] Anand KJ. Pain, plasticity, and premature birth: a prescription for permanent suffering? Nat Med 2000;6(9):971–3.
[25] Haley DW, Grunau RE, Weinberg J, Keidar A, Oberlander TF. Physiological correlates of memory recall in infancy: vagal tone, cortisol, and imitation in preterm and full-term infants at 6 months. Infant Behav Dev 2010;33(2):219–34.
[26] Oberlander TF, Grunau RE, Whitfield MF, Fitzgerald C, Pitfield S, Saul JP. Biobehavioral pain responses in former extremely low birth weight infants at four months' corrected age. Pediatrics 2000;105(1):1–10.
[27] Slater R, Cantarella A, Gallella S, Worley A, Boyd S, Meek J, et al. Cortical pain responses in human infants. J Neurosci 2006;26(14):3662–6.
[28] Slater R, Cantarella A, Franck L, Meek J, Maria Fitzgerald M. How well do clinical pain assessment tools reflect pain in infants? PLoS Med 2008;5(6):928–33.
[29] Fitzgerald M, Shaw A, MacIntosh N. Postnatal development of the cutaneous flexor reflex: comparative study of preterm infants and newborn rat pups. Dev Med Child Neurol 1988;30(4):520–6.
[30] Andrews K, Fitzgerald M. The cutaneous withdrawal reflex in human neonates: sensitization, receptive fields, and the effects of contralateral stimulation. Pain 1994;56(1):95–101.

[31] Slater R, Cantarella A, Yoxen J, Patten D, Potts H, Meek J, et al. Latency to facial expression change following noxious stimulation in infants is dependent on postmenstrual age. Pain 2009;146(1–2):177–82.
[32] Fitzgerald M, Millard C, MacIntosh N. Hyperalgesia in premature infants. Lancet 1988;1(8580):292.
[33] Abdukaldar HM, Freer Y, Fleetwood-Walker SM, MacIntosh N. Bodily progression of motor responses to increasing mechanical force stimulation in the newborn infant and the effect of heel prick. Neonatology 2008;94(1):38–44.
[34] Taddio A, Shah V, Atenafu E, Katz J. Influence of repeated painful procedures and sucrose analgesia on the development of hyperalgesia in newborn infants. Pain 2009;144(1–2):43–8.
[35] Gradin M, Finnström O, Schollin J. Feeding and oral glucose—additive effects on pain reduction in newborns. Early Hum Dev 2004;77(1–2):57–65.
[36] Eriksson M, Gradin M, Schollin J. Oral glucose and venepuncture reduce blood sampling pain in newborns. Early Hum Dev 1999;55(3):211–8.
[37] Slater R, Cornelissen L, Fabrizi L, Patten D, Yoxen J, Worley A, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet Sep. 1 2010 Early Online Publication.
[38] Lasky RE, van Drongelen W. Is sucrose an effective analgesic for newborn babies? Lancet Sep. 1 2010 Early Online Publication.
[39] Roeggen I, Harrison D, Johnston L, Boyce S, Loughnan P, Storm H, et al. Skin conductance variability between and within hospitalised infants at rest. Abstr Paediatr Child Health 2007;43(1).
[40] Johnston CC, Stevens BJ. Experience in a neonatal intensive care unit affects pain response. Pediatrics 1996;98(5):925–30.
[41] Herrington CJ, Olomu IN, Geller SM. Salivary cortisol as indicators of pain in preterm infants: a pilot study. Clin Nurs Res 2004;13(1):53–68.
[42] Slater R, Fabrizi L, Worley A, Meek J, Boyd S, Fitzgerald M. Premature infants display increased noxious-evoked neuronal activity in the brain compared to healthy age-matched term-born infants. Neuroimage 2010;52:583–9.
[43] Simons SHP, Tibboel D. Pain perception development and maturation. Semin Fetal Neonatal Med 2006;11(4):227–31.
[44] Porter FL, Grunau RE, Anand KJ. Long-term effects of pain in infants. J Dev Behav Pediatr 1999;20(4):253–61.
[45] Stevens B, Pillai Riddell RR, Oberlander TE, Gibbins S. Assessment of pain in neonates and infants. In: Anand KJS, Stevens BJ, McGrath PJ, editors. Pain in neonates and infants. 3rd ed. Toronto: Elsevier; 2007. p. 67–90.